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IODINATED BENZOFURANS AS THYROXINE ANALOGUES

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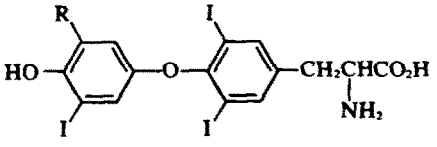
Abstract—Castro's synthesis of 2-arylbenzofurans has been extended to the reaction of 4-substituted-2,6-diiodophenols with selected cuprous phenyl acetylides to prepare some iodinated 2-aryl-benzofurans as potential thyroxine analogues.

The structure of the thyroid hormone thyroxine (1) has been extensively modified over the last few decades in a search for clinically useful compounds.[1] In order to achieve high thyromimetic activity, it is essential that certain substitution criteria are fulfilled. For example, when the iodine atom in the outer ring* of triiodothyronine (2) is replaced by an isopropyl group, the resultant molecule exhibits higher biological activity than thyroxine. The ethereal O atom can be replaced by a S atom,[2] or a carbonyl[3a] or a methylene group[3] with retention of some thyromimetic activity. Other linking groups often cause a dramatic reduction or loss of activity.[4]

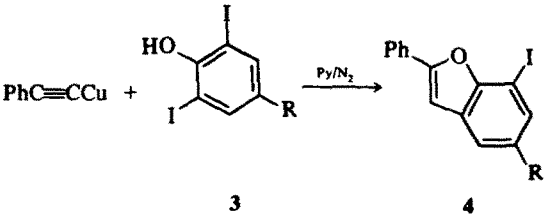


1: R = I
2: R = H

We have used Castro's method[5] to prepare analogues wherein the two phenyl rings are connected via a furan ring. This sets the two phenyl rings in planes which are different from those in the normal conformation of the thyroxine molecule. However, we hoped that even if the analogues were only weakly thyromimetic, they might exhibit the selective action we have been seeking.[6]

Castro *et al.* only used monoiodophenols in their synthesis of 2-phenylbenzofurans, although the heterocycle 3,5 - diiodo - 4 - hydroxypyridine gave an 86% yield of an iodofuro[[3,2-c]pyridine.[5b] We required to use 2,6-diiodophenols for the synthesis of thyroxine analogues and to test the generality of the synthetic method before proceeding to molecules closer to the thyroxine structure, we reacted the readily available cuprous phenylacetylide with the 4 - substituted - 2,6 - diiodophenols **3**. The 2-phenylbenzofurans **4** were isolated in moderate yield, indicating that the approach was feasible.

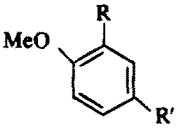
In order for the final benzofurans to contain "thyroactive" substituents, we then prepared 4-methoxy and 3 - isopropyl - 4 - methoxyphenylacetylene as intermediates.



3 **4**

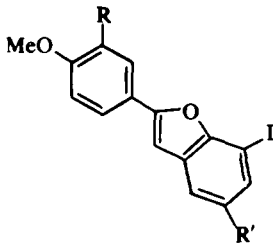
a: R = CHO
b: R = CH_2CO_2Me
c: R = CH_2CHCO_2Me (NHAc)

We used the method of Bodendorf *et al.*, briefly reported in 1963[7] but never fully exemplified for para methoxylated phenylacetylenes.[8] Thus, the acetophenones **5** and **6**[9] were treated with the Vilsmeier-complex derived from phosphoryl chloride and dimethylformamide to yield, after hydrolysis with aqueous sodium acetate, the intermediate chloro cinnamaldehydes. These were cleaved with sodium hydroxide in aqueous dioxan giving the phenylacetylenes **7** and **8** in low (*ca* 15%) yield, indicating that this arylacetylene synthesis is not particularly suitable for *para* methoxylated derivatives. These acetylenes were converted to their cuprous salts by the method used for phenylacetylene.[5b] DMF was the best solvent for conversion of the cuprous acetylides to the benzofurans **9–12**, which were obtained in moderate yield. The acids **13–16** were prepared by simple hydrolysis as additional compounds for biological testing. However, none of them exhibited any significant thyromimetic effect.



5: R = H, R′ = $COCH_3$
6: R = i-Pr, R′ = $COCH_3$
7: R = H, R′ = C≡CH
8: R = i-Pr, R′ = C≡CH

*The outer ring is defined as the benzene ring distal to the amino acid group.



9: R = H, R′ = CH_2CO_2Me
10: R = i-Pr, R′ = CH_2CO_2Me
11: R = H, R′ = CH_2CHCO_2Me (NHAc)
12: R = i-Pr R′ = CH_2CHCO_2Me (NHAc)

13: R = H, R′ = CH_2CO_2H
14: R = H, R′ = CH_2CHCO_2H (NHAc)
15: R = H, R′ = CH_2CHCO_2H (NH_2)
16: R = i-Pr, R′ = CH_2CHCO_2H (NHAc)

EXPERIMENTAL

Pyridine was stored over KOH, and DMF over molecular sieves prior to use. M.ps were determined on a Büchi-Tottoli apparatus and are uncorrected. IR spectra were measured as Nujol mulls; NMR spectra (60 MHz) were measured in $CDCl_3$ except where stated and chemical shifts (δ) are given relative to TMS as internal standard.

Methyl 4 - *hydroxy* - 3,5 - *diiodophenylacetate* (**3b**). 4 - Hydroxy - 3,5 - diiodophenylacetic acid[10] (130 g) was stirred in MeOH (1 l.) containing conc H_2SO_4 (50 ml) for 4 hr at room temp. The mixture was filtered, diluted with water and the product collected, yield 100 g, m.p. 130–133° after recrystallisation from MeOH aq (Found: C, 26·1; H, 1·9. $C_9H_8I_2O_3$ requires: C, 25·8; H, 1·9%).

4-Methoxyphenylacetylene (**7**). $POCl_3$ (153 ml) was added to DMF (181 ml) with stirring and cooling in an ice-bath so as to maintain the temp. in the range 10–20°. When the addition was complete, the mixture was allowed to come to room temp. when a solution of 4-methoxyacetophenone (100 g) in THF (420 ml) was added dropwise. A delayed exotherm was noticed and the maximum temp. attained was 53° during the 70 min addition. After stirring overnight at room temp., ether (500 ml) was added and after thorough mixing, the mixture was transferred to a separating funnel from which the lower layer was added as a slow stream to a vigorously stirred soln of sodium acetate trihydrate (140 g) in water (500 ml). After 3 hr at 25°, the mixture was stored in a refrigerator overnight. The crystals were collected and recrystallised from hexane (600 ml) affording the intermediate chloroaldehyde, 26·3 g, m.p. 62–5°.

This intermediate was dissolved in dioxan (200 ml) and added dropwise with stirring during 1 hr to a soln of NaOH (11·7 g) in water (120 ml) at reflux. The red-brown soln was refluxed for 1 hr, cooled and the organic product extracted with ether. Evaporation *in vacuo* gave a brown oil which was distilled *in vacuo*, yield 13·6 g, b.p. 80–81°/9 mm (lit.[11] b.p. 85–88°/11 mm). The yellow cuprous acetylide was prepared in 92% yield following Castro's procedure for phenylacetylene[5b] (Found: C, 55·4; H, 3·7. C_9H_7OCu requires: C, 55·6; H, 3·6%).

3 - *Isopropyl* - 4 - *methoxyphenylacetylene* (**8**). This compound was prepared in 17% yield (b.p. 88–96°/2 mm, 95% pure by glc) from **6** and converted to its orange copper salt in a method similar to that described above, except that the intermediate chloroaldehyde was not isolated in this case.

7 - *Iodo* - 2 - *phenylbenzofuran* - 5 - *carbaldehyde* (**4a**). 3,5 - Diiodo - 4 - hydroxybenzaldehyde[12] (5·0 g) was suspended in pyridine (40 ml) under N_2. Cuprous phenylacetylide (2·25 g) and pyridine (20 ml) were added and the mixture heated at 120° for 22 hr under N_2. After cooling, the residue was concentrated *in vacuo*, treated with water (70 ml) and ether (70 ml), filtered and the filter cake washed with ether. After extraction, the combined ether layers were washed with 1% HCl, 5% $NaHCO_3$ and water. After drying (Na_2SO_4) and evaporating *in vacuo*, the residue was treated with charcoal in EtOH and evaporated. The solid was recrystallised from light petroleum (b.p. 80–100°) then MeOH aq to yield 1·2 g (26%) of the title compound m.p. 143–6°. NMR 7·7 (1H, s, furan CH), 9·9 (1H, s, CHO) (Found: C, 51·8; H, 2·6. $C_{15}H_9IO_2$ requires: C, 51·7; H, 2·6%).

Methyl 2 - (7 - *iodo* - 2 - *phenylbenzofuran* - 5 - *yl*)*acetate* (**4b**). This was prepared in 44% yield in the same manner as for the foregoing compound from cuprous phenylacetylide and methyl 4 - hydroxy - 3,5 - diiodophenylacetate. It was obtained from light petroleum (b.p. 40–60°) and had m.p. 86–88°. IR 1730 cm^{-1}; NMR 3·71 (2H, s, $PhCH_2$), 3·76 (3H, s, CH_3), 7·13 (1H, s, furan CH), 7·54–8·0 (7H, 2m, aromatics) (Found: C, 52·3; H, 3·6. $C_{17}H_{13}IO_3$ requires: C, 52·1; H, 3·3%).

L - *Methyl* 2 - *acetamido* - 3 - (4 - *iodo* - 2 - *phenylbenzofuran* - 5 - *yl*)*propionate* (**4c**). This was prepared in 32% yield as above from cuprous phenylacetylide and N - acetyl - 3,5 - diiodo - L - tyrosine methyl ester.[13] An analytical sample was obtained from MeOH aq and had m.p. 178–180°. IR 3300, 1740, 1650 cm^{-1}; NMR 1·96 (3H, s, $COCH_3$), 3·1 (2H, d, CH_2CH), 3·65 (3H, s, OCH_3), 4·8 (1H, m, CH_2CH), 6·0 (1H, bs, NH), 6·9 (1H, s, furan CH), 7·3–7·7 (7H, 2m, aromatics) (Found: C, 52·0; H, 3·9; N, 3·25. $C_{20}H_{18}INO_4$ requires: C, 51·8; H, 3·9; N, 3·0%).

Methyl 2 - [7 - *iodo* - 2 - (4 - *methoxyphenyl*)*benzofuran* - 5 - *yl*]*acetate* (**9**). This was prepared from 4-methoxy cuprous phenylacetylide and methyl 4 - hydroxy - 3,5 - diiodophenylacetate in 16% yield after chromatography in toluene on silica gel. In this case DMF was used as reaction solvent. The product had m.p. 96–7° after recrystallisation from EtOH. IR 1720 cm^{-1}; NMR 3·68 (2H, s, CH_2), 3·75 and 3·85 (6H, 2s, OCH_3), 6·9–7·9 (7H, m, aromatics) (Found: C, 51·2; H, 3·6. $C_{18}H_{13}IO_4$ requires: C, 51·2; H, 3·6%).

Hydrolysis of **9** (1·4 g) with 5% KOH in 90% EtOH/H_2O (30 ml) at 40° for 1 hr gave the acid **13** m.p. 211–212° after recrystallisation from acetone aq. IR 3100–2300, 1715 cm^{-1}; NMR 3·6 (2H, s, CH_2), 3·8 (3H, s, OCH_3), 7·0–7·9 (7H, m, aromatics) (Found: C, 50·3; H, 3·4. $C_{17}H_{13}IO_4$ requires: C, 50·0; H, 3·2%).

L - *Methyl* 2 - *acetamido* - 3 - [7 - *iodo* - 2 - (4 - *methoxyphenyl*) - *benzofuran* - 5 - *yl*]*propionate* (**11**). This was prepared in 18% yield from 4-methoxy cuprous phenylacetylide and N - acetyl - 3,5

- diiodo - L - tyrosine methyl ester as for the foregoing compound. An analytical sample was obtained from EtOH and had m.p. 183–184°. IR 3300, 1745, 1730, 1660 cm^{-1}; NMR 1·98 (3H, s, $COCH_3$), 3·15 (2H, d, CH_2CH), 3·72 and 3·82 (6H, 2s, OCH_3), 4·6–5·0 (1H, m, CH_2CH), 6·2 (1H, d, NH), 6·85–7·85 (7H, m, aromatics) (Found: C, 51·0; H, 4·1; N, 3·1. $C_{21}H_{20}INO_5$ requires: C, 51·1, H, 4·0; N, 2·8%).

Hydrolysis of **11** (1·3 g) with KOH (1·2 g) in EtOH (60 ml) and water (5 ml) gave the N-acetyl acid **14**. Yield 0·72 g, m.p. 245–246° dec. Recrystallisation from AcOH aq gave the analytical sample m.p. 242–244° dec. IR 3300, 3100–2300, 1700, 1640 cm^{-1}; NMR (TFA) 2·18 (3H, s, $COCH_3$), 3·35 (2H, bs, CH_2CH), 4·05 (3H, s, OCH_3), 4·9–5·3 (1H, b, CH_2CH), 6·9–8·0 (7H, m, aromatics) (Found: C, 49·8; H, 3·8; N, 2·9. $C_{20}H_{18}INO_5$ requires: C, 50·1; H, 3·7; N, 2·9%).

Hydrolysis of **11** (1·5 g) with AcOH (15 ml) and conc HCl (15 ml) for 2 hr at reflux followed by cooling, precipitation with water and recrystallisation from AcOH aq gave the amino acid **15**. yield 0·55 g, m.p. 228–231°. IR 3100–2300, 1700 cm^{-1}; NMR (TFA) 3·2–3·7 (2H, b, CH_2CH), 4·0 (3H, s, OCH_3), 4·6–4·7 (1H, b, CH_2CH), 6·9–8·0 (7H, m, aromatics) (Found: C, 49·6; H, 3·8; N, 3·0. $C_{18}H_{14}INO_4$ requires: C, 49·5; H, 3·7; N, 3·2%).

Methyl 2 - [7 - iodo - 2 - (3 - isopropyl - 4 - methoxyphenyl) - benzofuran - 5 - yl]acetate (**10**). This was prepared in 63% yield from 3 - isopropyl - 4 - methoxy cuprous phenylacetylide and methyl 4 - hydroxy - 3,5 - diiodophenylacetate as above. An analytical sample was obtained from EtOH and had m.p. 97–99°. IR 1740 cm^{-1}; NMR 1·25 (6H, d, $CH(CH_3)_2$), 3·2–3·4 (1H, m, $CH(CH_3)_2$), 3·65 (2H, s, CH_2CO), 3·70 and 3·88 (6H, 2s, OCH_3), 6·8–7·8 (6H, m, aromatics) (Found: C, 54·4; H, 4·7. $C_{21}H_{21}IO_4$ requires: C, 54·3; H, 4·5%).

L - *Methyl 2 - acetamido - 3 - [7 - iodo - 2 - (3 - isopropyl - 4 - methoxyphenyl) - benzofuran - 5 - yl]propionate* (**12**). This was prepared in 40% yield from 3 - isopropyl - 4 - methoxy cuprous phenylacetylide and N - acetyl - 3,5 - diiodo - L - tyrosine methyl ester. An analytical sample had m.p. 156–158° after recrystallisation from EtOH. IR 3300, 1745, 1725, 1650 cm^{-1}; NMR 1·30 (6H, d, $CH(CH_3)_2$), 2·0 (3H, s, $COCH_3$), 3·1 (2H, d, CH_2CH), 3·1–3·5 (1H, m, $CH(CH_3)_2$, 3·8 and 3·9 (6H, 2s, OCH_3), 4·8 (1H, m, CH_2CH), 6·8–7·8 (6H, m, aromatics) (Found: C, 53·9; H, 5·0; N, 2·7. $C_{24}H_{26}INO_5$ requires: C, 53·8; H, 4·9; N, 2·6%).

Hydrolysis of **12** (2·0 g) with KOH (2·1 g) in EtOH (60 ml) and water (10 ml) during 2 min gave the N-acetyl acid **16**, yield 0·85 g, m.p. 177–180°. IR 3350, 3100–2300, 1720, 1620 cm^{-1}; NMR (CD_3SOCD_3), 1·25 (6H, d, $CH(CH_3)_2$), 1·85 (3H, s, $COCH_3$), 3·0–3·5 (3H, m, CH_2CH and $CH(CH_3)_2$), 3·9 (3H, s, OCH_3), 4·3–4·7 (1H, bm, CH_2CH), 6·8–7·8 (6H, m, aromatics), 8·1–8·3 (1H, b, NH) (Found: C, 52·8; H, 4·6; N, 2·8. $C_{23}H_{24}INO_5$ requires: C, 53·0; H, 4·6; N, 2·7%).

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